REMARKS

1. Formal Matters

a. Status of the Claims

Claims 1, 3, 6, 8, 9, 12, 13, and 18 are pending in this application. Claims 1, 3, 6, 8, 9, 12, 13, and 18 are hereby canceled without prejudice to pursuing the canceled subject matter in a continuing application; and claims 21-34 are new. Upon entry of these amendments, claims 21-34 are pending and under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

b. Interview Summary

The undersigned would like to thank Examiners Shin and Zara for the courtesy of the personal interview on May 8, 2007 during which the prior art and amendments to the claims were discussed. This Reply is filed to address the issues raised by the Examiner.

c. Amendments to the Claims

New claim 21 is related to an isolated viral miRNA, which is the product of a viral hairpin. New claim 21 recites an isolated first viral nucleic acid or complement thereof, support for which can be found at claim 12 as originally filed in a preliminary amendment filed the day of the 35 U.S.C. § 371 filing date.

New claim 21, limitation (a) recites that the first viral nucleic acid (*i.e.*, miRNA) consists of 17 to 24 nucleotides, support for which can be found at Table 3 of the application as originally filed. One thousand seven hundred and ninety-seven miRNAs disclosed in the instant application have a length in this length range. For example, SEQ ID NO: 2458 is a viral miRNA is 17 nucleotides in length. This sequence is disclosed in Table 3, line 1634 of the application as originally filed, as follows:

GENE NAME	VGAM SEQ-ID	GENE_SEQUENCE (5`_TO_3`)	PRECUR SEQ-ID	SOURCE REF-ID	SRC	VGAM ACC
VGAM2177.2	2458	GGGGGCTGAAGAAGGAC	84	NC_002512	100	

Support for limitation (a) can also be found at the paragraph beginning on page 4, line 29 of the specification as originally filed, which in part recites "viral gene is about 18 to about 24 nucleotides in length."

New claim 21, limitation (b) recites that a second viral nucleic acid (*i.e.*, RNA precursor hairpin or stem-loop structure) consisting of 50 to 131 nucleotides comprises the first viral nucleic acid, support for which can be found at the paragraph beginning on page 4, line 29 of the specification as originally filed. This paragraph in part recites, "RNA precursor is about 50 to about 120 nucleotides in length..." Support for limitation (b) can also be found at SEQ ID NO: 644, which is a viral hairpin that is 131

nucleotides in length. This sequence is disclosed in Table 2, lines 253-261 of the application as originally filed, as follows:

```
GENE NAME   PRECUR PRECURSOR-SEQUENCE    FOLDED-PRECURSOR                                                    SRC VGAM
            SEQ-ID (5`_TO_3`)                                                                                ACC
---------- ------ ----------------- ------------------------------------------------------------          --- -----

VGAM79      644    AATGTCAACCGCTTCAATGT      CAA    TTCA--      C   CACAA    AA--       G  T     G   101  C
                   GGCTATCACAAGGGCAAAAA AATGT   CCGC       ATGTGG TAT      GGGC     AAATTG CA TTTGT CA
                   TTGGGATTTTGTGGATAATG TTACA   GGTG       TGCACC ATA      TCTG     TTTAAC GT AAACA GT
                   TCTGATAGAGATCTTTATGA       TC-    TAACGC       -   AAGA-    AACA      -  C     -
                   CAAACTGCAATTTACAAGTC    T-    GATAG
                   TAGAAATACCACGTCGCAAT TAA  GTCT
                   GTGGCTACATT           ATT  TAGA
                                           TC    -----
```

New claim 21, limitation (c) recites that the second viral nucleic acid is capable of forming a hairpin, support for which can be found at the paragraph beginning on page 4, line 29 of the specification as originally filed. This paragraph in part recites, "a nucleotide sequence of a first half of the RNA precursor is a partial inversed-reversed sequence of a nucleotide sequence of a second half thereof…"

Part (i) of limitation (c) of new claim 21 recites that the hairpin comprises two stem segments and an intervening loop, support for which can be found at the Table 2 of the application as originally filed. Table 2 shows diagrams depicting stem-loop structures of the claimed nucleic acids. For example, Table 2, lines 2030-2034 discloses the following structure for the nucleic acid as set forth in SEQ ID NO: 867 (the loop is in bold underline):

```
GENE NAME   PRECUR PRECURSOR-SEQUENCE    FOLDED-PRECURSOR                                                    SRC VGAM
            SEQ-ID (5`_TO_3`)                                                                                ACC
---------- ------ ----------------- ------------------------------------------------------------          --- -----
VGAM677     867    CCATTAATATCTCTATTATA          ATCTCTATTATAGCT     AC     TCATCT                        100
                   GCTTCTGGACATAATTCATC CCATTAAT                  TCTGG  ATAAT
                   TATTATACCAGAATTAATGG GGTAATTA                 AGACC  TATTA
                                          ---------------      A-      ------
```

Part (ii) of limitation (c) of new claim 21 recites that the two stem segments each consist of 19 to 71 nucleotides, support for which can be found at Table 2 of the application as originally filed. One thousand five hundred and ninety-three stem-loop structures disclosed in the instant application have stem segments in this length range. For example, Table 2, lines 2030-2034 as shown above discloses that the stem-loop structure for the nucleic acid as set forth in SEQ ID NO: 867 has a stem segment that is 19 nucleotides in length.

Table 2, lines 8569-8577 also discloses that the stem-loop structure for the nucleic acid as set forth in SEQ ID NO: 251 has a stem segment that is 71 nucleotides in length, as follows (the stem segment is in bold):

```
  CT  G      G      T    -    T ------     C-      ------------    A  C    TATCTT
TG  AG CCGCCT TTGTGG GGAT ACTG C       GCCCC  ACTGA             TCC TC ATTG
AC  TT GGTGGG GACACC CTTA TGAC G       CGGGG  TGACT             AGG AG TAAT
  TT  G      A      -    A    C CTTCCT     TC     TATTATGATGAA   -  T    ------
```

Part (iii) of limitation (c) of new claim 21 recites that the loop segment consists of 3 to 19 nucleotides, support for which can be found at Table 2 of the application as originally filed. One thousand five hundred and ninety-three stem-loop structures disclosed in the instant application have a loop segment in this length range. Table 2, lines 37-41 discloses that the stem-loop structure for the nucleic acid as set forth in SEQ ID NO: 625 has a loop that is 3 nucleotides in length, as follows (the loop is in bold underline):

```
GENE NAME  PRECUR PRECURSOR-SEQUENCE   FOLDED-PRECURSOR                                                    SRC VGAM
           SEQ-ID (5`_TO_3`)                                                                              ACC
---------- ------ ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- --- -----
VGAM8      625    AAACGCGGGCGTATTGGTCC          C  A          AT   --   -   G  G  GTA                    100  C
                  CAATGGGGTCTCGGTGGGGT AAACGCGGG GT TTGGTCCCA  GG  GGT CTC GT GG
                  ATCGACAGAGTGCCAGCCCT TTTGCGCCC CA AGCCAGGGT  CC  CCG GAG CA CT
                  GGGACCGAACCCCGCGTTT          -  -          C-  GA   T   A  G  ---
```

Table 2, lines 7507-7512 also discloses that the stem-loop structure for the nucleic acid as set forth in SEQ ID NO: 1302 has a loop that is 19 nucleotides in length, as follows (the loop is in bold underline):

```
GENE NAME  PRECUR PRECURSOR-SEQUENCE   FOLDED-PRECURSOR                                                    SRC VGAM
           SEQ-ID (5`_TO_3`)                                                                              ACC
---------- ------ ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- --- -----
VGAM2526   1302   TATAATGTACTAGATAATAT     A  T    GA         TAAAG-     ATTTAACCAACCTATCTTC             100  D
                  TATAAAGCCTTTATTTAACC TATA TG ACTA  TAATATTA       CCTTT
                  AACCTATCTTCAAAGGACCG ATAT GC TGGT  ATTGTAGT       GGAAA
                  TCTGATGTTAAATGGTTCGA     A  T    AA         CTGCCA      --------------------
                  TATA
```

Limitation (iv) of limitation (c) of new claim 21 recites that the first and second stem segment are at least 44.1% complementary, support for which can be found at Table 2 of the application as originally filed. One thousand five hundred and ninety-two of the stem-loop structures disclosed in the instant application have a first and second stem segment that are at least 44.1% complementary. For example, Table 2, lines 6086-6090 discloses that the stem-loop structure for the nucleic acid as set forth in SEQ ID NO: 57 has a stem in which 44.1% of the nucleotides are complementary, as follows:

```
GENE NAME  PRECUR PRECURSOR-SEQUENCE   FOLDED-PRECURSOR                                                    SRC VGAM
           SEQ-ID (5`_TO_3`)                                                                              ACC
---------- ------ ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- --- -----
VGAM2060   57     GGTGTGAATATCAAGCAGGA      GAATATCAA-  -  GA-  TAACAAG    GATCT                       101
                  CATAACAAGGTAGGATCTCT GGTGT          GC AG   CA        GTAG
                  ACAATACTTGGCACTAGCAG CCACA          CG TC   GT        CATC
                  CATTAATAACACC             ATAATTACGA  A  ACG  TCATAA-   -----    -
```

Limitation (v) of limitation (c) of new claim 21 recites that one of the stem segments of the hairpin comprises the first viral nucleic acid, support for which can be found at the paragraph beginning on page 4, line 29 of the specification as originally filed. This paragraph in part recites, "…RNA encoded

by the bioinformatically detectable novel viral gene is about 18 to about 24 nucleotides in length, and originates from an RNA precursor..."

Limitation (d) of new claim 21 recites that the first viral nucleic acid is capable of binding to a binding site of a mRNA, support for which can be found at the paragraph beginning on page 4, line 29 of the specification as originally filed. This paragraph in part recites, "...a nucleotide sequence of the RNA encoded by the novel viral gene is a partial inversed-reversed sequence of a nucleotides sequence of a binding site associated with at least one host target gene..."

Limitation (e) of new claim 21 recites that the first viral nucleic acid is capable of inhibiting expression of a protein encoded by a RNA, wherein the RNA comprises the binding site, support for which can be found at the paragraph beginning on page 6, line 1 of the specification as originally filed. This paragraph in part recites, "...the RNA encoded by the novel viral gene complementarily binds the binding site associated with the at lest one target host gene, thereby modulating expression of the at least one target host gene."

New claim 22 recites the nucleic acid of claim 21, wherein in the first viral nucleic acid is at least 72.7% complementary to the mRNA, support for which can be found at Table 4 of the application as originally filed. One thousand seven hundred and seventy-five miRNAs disclosed in the instant application are at least 72.7% complementary to a target mRNA. For example Table 4, lines 350919-3520925 shows that 16 out of 22 (72.7%) nucleotides of the miRNA as set forth in SEQ ID NO: 2964 are sufficient to bind the target gene LOC20314, as follows:

GENE NAME	VGAM SEQ-ID	TARGET	#BS	TARGET SEQ-ID	TARGET REF-ID	UTR	UTR OFFSET	TAR- BS-SEQ	BINDING-SITE-DRAW (UPPER:VGAM;LOWER:TARGET)	SRC	VGAM ACC	BS ACC	TAR ACC
VGAM934.1	2964	LOC2034 1	1	234992	XP_114697. 3	702		CAGTCT	CTTCGC	101	C	A	A
								GTCAGT	TTAATGTACA CTGACG				
								TACACT	GATTACATGT GACTGT				
								GTACAT	CACATT				
								TAGGGA					
								TA					

New claim 23 recites the nucleic acid of claim 21, wherein the untranslated region of the mRNA comprises the binding site, support for which can be found at the paragraph beginning on page 6, line 4 of the specification as originally filed. This paragraph in part recites, "the binding site associated with at least one target host gene is located in an untranslated region of RNA encoded by the at least one target host gene."

New claim 24 recites the nucleic acid of claim 21, wherein the hairpin is characterized by a negative free energy of folding of at least -11.3 Kcal/mol, support for which can be found at Table 2, lines 6086-6090 of the application as originally filed. As described above, Table 2 shows that the sequence as set forth in SEQ ID NO: 57 forms a stem-loop structure. According to the method for calculating free

folding energy as described in Mathews *et al.* (*J Mol Biol*, 1999;288(5):911-40), the free energy of folding of this stem-loop structure is -11.3 Kcal/mol. One thousand five hundred twenty-six stem loop structures disclosed in the specification have a negative free energy of folding of at least -11.3 Kcal/mol.

New claim 25 recites the nucleic acid of claim 21, wherein the mRNA is transcribed from the genome of the host of the virus, support for which can be found as described for new claim 23.

New claim 26 recites the nucleic acid of claim 21, wherein the first viral nucleic acid and the mRNA are in different parts of a genome, support for which can be found throughout the specification as originally filed. Claim 21 is related to viral nucleic acids. As described in the paragraph beginning on page 4, line 1 of the specification as originally filed, the viral nucleic acids are related to regulatory RNAs that are capable of repressing expression of host target host genes. The viral nucleic acids and the target genes are thus from different parts of a genome.

New claim 27 recites the nucleic acid of claim 21, wherein the viral nucleic acid is from a DNA virus, support for which can be found at Table 1 of the application as originally filed. Table 1 lists 26 DNA viruses, including human adenoviruses A-F and human herpesviruses 1-8.

New claim 28 recites the nucleic acid of claim 27, wherein the virus is selected from the group consisting of: human adenovirus, adeno-associated virus, B19 virus, human herpesvirus, human papillomavirus, molluscum contagiosum virus, ovine adenovirus, rat cytomegalovirus, vaccinia virus and variola virus, support for which can be found at Table 1 of the application as originally filed.

New claim 29 recites the nucleic acid of claim 21, wherein the viral nucleic acid is from a RNA virus, support for which can be found at Table 1 of the application as originally filed. Table 1 lists 55 RNA viruses, including hepatitis A, C, D, and E.

New claim 30 recites the nucleic acid of claim 29, wherein the virus is selected from the group consisting of: Barmah forest virus, Borna disease virus, bovine kobuvirus, Colorado tick fever virus, dengue virus, Eastern equine encephalitis virus, Encephalomyocarditis virus, equine rhinovirus, hepatitis virus, human astrovirus, human coronavirus, human echovirus, human enterovirus, human metapneumovirus, human parainfluenza virus, human respiratory syncytial virus, human rhinovirus, influenza virus, Japanese encephalitis virus, Marburg virus, measles virus, Murray valley encephalitis virus, Norwalk virus, poliovirus, respiratory syncytial virus, reston Ebola virus, rubella virus, salmon pancreas disease virus, SARS coronavirus, simian picornavirus 1, Sindbis virus, sleeping disease virus, tick-borne encephalitis virus, transmissible gastroenteritis virus, West Nile virus, Western equine encephalomyelitis virus, Yellow Fever virus and Zaire Ebola virus, support for which can be found at Table 1 of the application as originally filed.

New claim 31 recites the nucleic acid of claim 29, wherein the viral nucleic acid is a retrovirus, support for which can be found at Table 1 of the application as originally filed. Table 1 lists four retroviruses, including HIV1 and HIV2.

New claim 32 recites the nucleic acid of claim 31, wherein the virus is selected from the group consisting of: human immunodeficiency virus 1, human immunodeficiency virus 2, human T-lymphotropic virus 2 and simian immunodeficiency virus.

New claim 33 recites a probe comprising a nucleic acid according to any one of claims 21-32, support for which can be found at the paragraph beginning on page 6, line 22 of the specification as originally filed. This paragraph in part recites, "the invention includes a probe including the DNA."

New claim 34 recites a vector comprising a nucleic acid according to any one of claims 21-32, support for which can be found at the paragraph beginning on page 6, line 11 of the specification as originally filed. This paragraph recites in part, "the invention includes a vector including the DNA."

New claims 35-49 are directed to precursor nucleic acids comprising viral miRNAs, support for which is parallel with corresponding claims 21-34. For example, similar to limitation (b) in claim 21, new claim 35, limitation (a) recites that a first nucleic acid (i.e., RNA precursor hairpin or stem-loop structure) consisting of 50 to 131 nucleotides comprise a second viral nucleic acid (i.e., miRNA), support for which can be found at the paragraph beginning on page 4, line 29 of the specification as originally filed. This paragraph in part recites, "RNA precursor is about 50 to about 120 nucleotides in length..." Support for limitation (a) can also be found at SEQ ID NO: 644, which is a viral hairpin that is 131 nucleotides in length. This sequence is disclosed in Table 2, lines 253-261 of the application as presented above on page 10.

d. Amendments to the Specification

The title of the application is amended to strike the term "novel."

The second paragraph after the heading "Brief Description of Sequence Listing, Large Tables and Computer Program Listing" at page 2, is amended to incorporate by reference the replacement Sequence Listing submitted herewith.

The paragraph beginning on page 9, line 9 is amended to assign SEQ ID NOs: 424577-424587 to the sequences shown in Fig. 14B in compliance with 37 C.F.R. §§ 1.821-1.825, support for which can be found at Fig. 14B as originally filed.

The paragraph beginning on page 9, line 16 is amended to assign SEQ ID NOs: 424572-424576 to the sequences shown in Fig. 15A in compliance with 37 C.F.R. §§ 1.821-1.825, support for which can be found at Fig. 15A as originally filed.

The paragraph beginning on page 9, line 23 is amended to assign SEQ ID NOs: 424588-424598 to the sequences shown in Fig. 16 in compliance with 37 C.F.R. §§ 1.821-1.825, support for which can be found at Fig. 16 as originally filed.

The paragraph beginning on page 36, line 4 is amended to assign SEQ ID NOs: 424599-424601 to the listed sequences in compliance with 37 C.F.R. §§ 1.821-1.825, support for which can be found at this paragraph as originally filed.

The paragraph beginning on page 36, line 25 is amended to assign SEQ ID NOs: 424602 and 424603 to the listed sequences in compliance with 37 C.F.R. §§ 1.821-1.825, support for which can be found at this paragraph as originally filed.

The paragraph beginning on page 36, line 29 is amended to assign SEQ ID NOs: 424604-424606 to the listed sequences in compliance with 37 C.F.R. §§ 1.821-1.825, support for which can be found at this paragraph as originally filed.

The paragraph beginning on page 41, line 18 is amended to assign SEQ ID NOs: 424607-424612 to the listed sequences in compliance with 37 C.F.R. §§ 1.821-1.825, support for which can be found at this paragraph as originally filed.

e. Amendments to the Abstract

The abstract is amended to strike the terms "novel" and to avoid use of legal phrases such as "thereof." The abstract is also amended to correct typographical errors.

2. Preliminary Remarks

a. Sequence Rule Compliance

On page 2 of the Office Action, the Examiner alleges that the instant application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825. The Examiner requires that the nucleic acid sequences shown on pages 36, 37, 41, and 42, and in Figures 14-16 be assigned sequence identifiers.

Applicant submits herewith a replacement Sequence Listing pursuant to 37 C.F.R. § 1.825(a), and the specification is amended to assign SEQ ID NOS to the disclosed nucleic acid sequence in accordance with 37 C.F.R. §§ 1.821-1.825 as required by the Examiner. No new matter has been added. In view of the amendments to the specification described above and the replacement sequence listing submitted herewith, Applicant respectfully submits that the application complies with 37 C.F.R. §§ 1.821-1.825.

b. Specification Informalities

On page 4 of the Office Action, the Examiner objects to the specification for including informalities. The Examiner asserts that the title and abstract of the instant application contain the term "novel." Applicant respectfully submits that, as described above, the instant abstract and specification are amended to strike this term.

The Examiner also asserts that the instant disclosure contains non-compliant sequences. As described above, Applicant respectfully submits that in view of the above-described amendments and replacement Sequence Listing, the instant application complies with 37 C.F.R. §§ 1.821-1.825.

The Examiner also requires that the abstract be corrected to avoid legal phrases such as the term "thereof." Applicant respectfully submits that, as described above, the abstract is amended as required by the Examiner.

3. Patentability Remarks

a. 35 U.S.C. § 112, 1st paragraph

On pages 4-7 of the Office Action, the Examiner rejects claims 9 and 18 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicant respectfully submits that claims 9 and 18 are canceled, thereby rendering the rejection moot.

b. 35 U.S.C. § 112, 2nd paragraph

On page 7 of the Office Action, the Examiner rejects claims 1, 3, 6, 8, 9, 12, 13, and 18 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicant respectfully submits that claims 1, 3, 6, 8, 9, 12, 13, and 18 are canceled, thereby rendering the rejection moot.

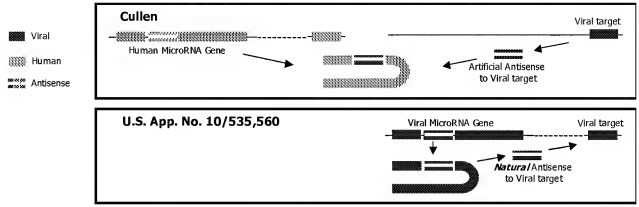
c. 35 U.S.C. § 102

Claims 1, 3, 6, 8, 12, and 13 over Cullen

On page 8 of the Office Action, the Examiner rejects claims 1, 3, 6, 8, 12, and 13 under 35 U.S.C. § 102(e) as allegedly being anticipated by Cullen *et al.* (U.S. Pub. Pat. Appl. No. 2004/0053411; "Cullen" hereafter). The Examiner asserts that Cullen teaches an isolated DNA encoding a miRNA that targets conserved sequences in viruses such as hepatitis C virus, papilloma virus and HIV. The Examiner concludes that Cullen teaches all the structural limitations of the claimed subject matter. Applicant respectfully disagrees.

New claims 21-34 are directed to viral nucleic acids that are capable of binding a target mRNA. The claimed viral nucleic acids may be found in region of a viral genome that is capable of forming a hairpin with certain claimed features of secondary structure. In contrast, the viral portion of the Cullen nucleic acid capable of targeting viral target sequences does not originate from a genomic region that is

capable of forming secondary structure comprising the claimed features. As shown in the figure below, the claimed nucleic acids originate from a different point in the viral genome from the target gene sequence whereas Cullen's viral nucleic acid sequence originates from the exact target gene sequence and this region is not capable of forming the requisite hairpin.



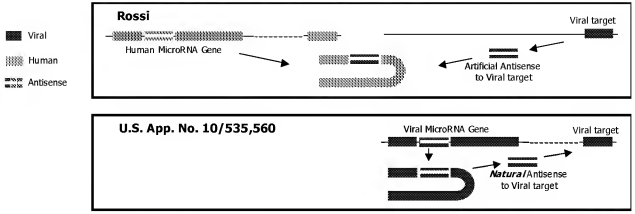
New claims 35-49 are directed to viral precursor nucleic acid sequences that are completely viral in nature. As show in the figure above and in contrast to claims 35-49, the hairpin nucleic acid of Cullen is not entirely viral because the viral target gene sequence of Cullen is cloned into a human hairpin sequence. Accordingly, the claimed nucleic acids are distinct from the Cullen nucleic acids. In view of the foregoing amendments and remarks, Applicant respectfully submits that a rejection of new claims 21-49 would be improper in view of Cullen under 35 U.S.C. § 102(e).

Claims 1, 3, 8, 12, and 13 over Rossi

On page 9 of the Office Action, the Examiner rejects claims 1, 3, 8, 12 and 13 under 35 U.S.C. § 102(e) as allegedly being anticipated by Rossi *et al.* (U.S. Pub. Pat. Appl. No. 2005/0074887; "Rossi" hereafter). The Examiner asserts that Rossi teaches a DNA construct encoding miRNA, shRNA, or other siRNA precursors that are targeted to the HIV-1 *rev* sequence and inhibit the expression of HIV-1. The Examiner concludes that Rossi teaches all the limitations of the claimed subject matter. Applicant respectfully disagrees.

New claims 21-34 are directed to viral nucleic acids that are capable of binding a target mRNA. The claimed viral nucleic acids may be found in region of a viral genome that is capable of forming a hairpin with certain claimed features of secondary structure. In contrast, the viral portion of the Rossi nucleic acid capable of targeting viral target sequences does not originate from a viral genomic region that is capable of forming secondary structure comprising the claimed features. As shown in the figure below, the claimed nucleic acids originate from a different point in the viral genome from the target gene

sequence whereas Rossi's viral nucleic acid sequence originates from the exact target gene sequence and this region is not capable of forming the requisite hairpin.

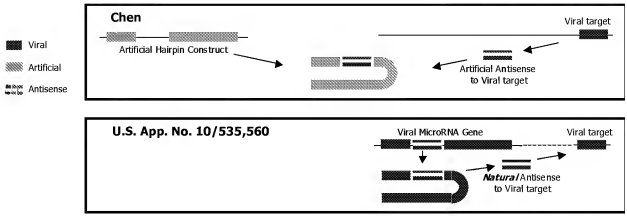


New claims 35-49 are directed to viral precursor nucleic acid sequences that are completely viral in nature. As show in the figure above and in contrast to claims 35-49, the hairpin nucleic acid of Rossi is not entirely viral because the viral target gene sequence of Rossi is cloned into a human hairpin sequence. Accordingly, the claimed nucleic acids are distinct from the Rossi nucleic acids. In view of the foregoing amendments and remarks, Applicant respectfully submits that a rejection of new claims 21-49 would be improper in view of Rossi under 35 U.S.C. § 102(e).

Claims 1, 3, 6, 8, 9, 12, 13, and 18 over Chen

On page 10 of the Office Action, the Examiner rejects claims 1, 3, 8, 12 and 13 under 35 U.S.C. § 102(e) as allegedly being anticipated by Chen *et al.* (U.S. Pub. Pat. Appl. No. 2004/0242518; "Chen" hereafter). The Examiner asserts that Chen teach shRNA and vectors encoding shRNA precursors that target influenza virus sequence. The Examiner concludes that Chen teaches all the limitations of the claimed subject matter. Applicant respectfully disagrees.

New claims 21-34 are directed to viral nucleic acids that are capable of binding a target mRNA. The claimed viral nucleic acids may be found in region of a viral genome that is capable of forming a hairpin with certain claimed features of secondary structure. In contrast, the artificial viral antisense sequence of Chen capable of targeting viral target sequences is replicated from a viral genomic region that is incapable of forming secondary structure comprising the claimed features. As shown in the figure below, the claimed nucleic acids originate from a different point in the viral genome from the target gene sequence whereas Chen's viral nucleic acid sequence originates from the exact target gene sequence and this region is not capable of forming the requisite hairpin.



New claims 35-49 are directed to viral precursor nucleic acid sequences that are completely viral in nature. As show in the figure above and in contrast to claims 35-46, the hairpin nucleic acid of Chen is not entirely viral because the artificial viral target gene sequence of Chen is cloned into a artificial hairpin sequence. Accordingly, the claimed nucleic acids are distinct from the Chen nucleic acids. In view of the foregoing amendments and remarks, Applicant respectfully submits that a rejection of new claims 21-49 would be improper in view of Chen under 35 U.S.C. § 102(e).

d. 35 U.S.C. § 103

On pages 10-12 of the Office Action, the Examiner rejects claims 1, 3, 6, 8, 12, and 13 under 35 U.S.C. § 103(a) as being unpatentable over Jacque, *et al.* (*Nature*, 2002;418:435-7; "Jacque" hereafter) in view of Hutvagner, *et al.* (*Science*, 2002;297:2056-60; "Hutvagner" hereafter), and Paillart *et al.* (*J. Biol. Chem.*, 2002;277:5995-6004; "Paillart" hereafter). The Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the HIV-1 shRNA molecules of Jacque to miRNA in view of the advantage of miRNAs over siRNAs as taught by Hutvagner, and targeting the 5'UTR of HIV-1 RNA that is critical for HIV replication as taught by Paillart. Applicant respectfully submits that the Examiner would be unable to establish a *prima facie* case of obviousness for new claims 21-32, 35-46, and 49 because (i) the cited references fail to teach or suggest all the claimed limitations; (ii) there is a lack of suggestion or motivation to combine the cited references; and (iii) the cited references do not provide a reasonable expectation of success.

(1) The Cited References Fail to Teach or Suggest All the Claim Limitations

To establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. *See* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The Examiner acknowledges that Jacque teaches synthetic plasmid-derived siRNAs targeted to regions of the HIV-1 genome, but fails to teach the general structural features of miRNAs and that the targeted HIV-1 target sequences are in untranslated regions. The Examiner alleges that Hutvagner and Paillart together remedy

the deficiencies of Jacque by teaching features of miRNAs and that miRNAs can function in the RNAi pathway, and that the 5'-untranslated region of HIV-1 RNA contains multiple regulatory regions of viral replication. Applicant respectfully disagrees.

Applicant respectfully submits that the viral siRNA sequence of Jacque is not completely viral in nature. Rather, the siRNA-based sequence of Jacque is a synthetic hybrid. In contrast, the miRNA/hairpin-related nucleic acids claims 21-32, 35-46, and 49 are entirely viral in nature. Accordingly, Jacque neither teaches or suggests the claim limitation that the first and second nucleic acids are from a viral genome.

Hutvagner does not remedy the deficiency of Jacque's failing to teach viral miRNA/hairpin nucleic acids because Hutvagner's miRNAs are derived from a metazoan genome. Paillart also fails to remedy the deficiency of both Hutvagner and Jacque because Paillart simply teaches the structure of HIV, and fails to teach or suggest the claimed nucleic acids. In view of Hutvagner and Paillart failing to remedy the deficiencies of Jacque, Applicant respectfully submits that the cited references fail to teach or suggest all the limitations of new claim 21.

(2) The Cited References Fail to Suggest or Motivate Combining Reference Teachings

To establish a *prima facie* case of obviousness, there must also be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. *See* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

On page 11 of the Office Action, the Examiner alleges that one of skill in the art at the time of the invention would have been motivated to modify the HIV-1 shRNA molecules of Jacque in view of Hutvagner and Paillart. Applicant respectfully disagrees. Jacque teaches using synthetic siRNAs wherein the sequence is partially derived from HIV genomic sequences. These synthetic siRNAs target regions of the HIV genome with certain structural features distinct from the nucleic acids of claims 21-32, 35-46, and 49. Applicant respectfully submits that the art at the time of filing, as evidenced by Patzel V, *et al* (*Nucleic Acids Research*, 1999;27(22);4328-34) and Schubert S, *et al* (J Mol Biol, 2005;348:883-93)("Schubert" hereafter), teaches that the design of siRNA required selection of target regions with little to no predicted secondary structure.[1] Consequently, an siRNA based upon genomic sequence and any genomic sequence flanking the siRNA sequence are derived from a region in the genome devoid of secondary structure. In stark contrast, the nucleic acids of claims 21-32, 35-46, and 49 are related to viral

miRNAs, and viral hairpins with certain secondary structures. Applicant submits that one of skill in the art at the time of invention would not have chosen genomic sequences for an siRNA from a genomic region that has secondary structure because the corresponding target gene sequence would also be capable of forming secondary structure. Accordingly, there would have been no motivation by one of skill to alter the teachings of Jacque in view of Hutvagner because Jacque's siRNA derived genomic sequences are devoid of secondary structure as well as the particular target gene genomic sequences. Even if Jacque designed synthetic miRNAs based upon Hutvager, the viral sequences of the synthetic miRNA disclosed in Jacque would still be derived from genomic sequence regions devoid of second structure. Paillart fails to remedy the lack of motivation of both Hutvager and Jacque because Paillart simply teaches targeting the 5'UTR region of HIV to affect replication. Applicant respectfully submits that the Examiner has failed to provide a rationale for making the claimed viral nucleic acids capable of forming secondary structure, especially in view of Jacque teaching using siRNAs to target viral target genes with no secondary structure. In view of the foregoing, Applicant respectfully submits that the cited reference fail to provide the necessary motivation or suggestion to combine the cited references.

(3) The Cited Reference Fail to Provide a Reasonable Expectation of Success

To establish a *prima facie* case of obviousness, there must also be a reasonable expectation of success. *See* In re Vaeck, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991). The Examiner alleges that since the HIV-1 shRNA molecule of Jacque reduces the level of HIV in infected cells, the skilled artisan would have had reasonable expectation of success in making miRNA molecules targeted to the 5'UTR region of HIV-1 RNA that modulates HIV-1 expression. In view of the foregoing amendments, Applicant respectfully disagrees because the Examiner has failed to provide a rationale for a reasonable expectation of success based on the cited references. A year and four months after the filing date of the instant application, the consensus in the art was that viral miRNAs were an entirely new discovery. Specifically, *Science's* commentary on the Pfeffer *et al.* (*Science,* 2004;304(5671):734-6) landmark paper states that "miRNAs have been found in the genomes of all plants and animals so far analyzed (the exceptions being some fungi). Pfeffer et al. now show the presence of miRNAs in a virus, the 'fourth domain' of life." See *Science,* 2004;304(5671):645-8. Accordingly, the consensus view of those skilled in the art was that viruses do not contain miRNAs. Jacque and Hutvagner exemplify this consensus by teaching using synthetic siRNA constructs, not viral-specific miRNAs, to target mRNAs. Paillart further lacks a teaching or suggestion to using viral miRNA to target host genes. Accordingly, one of skill would not have

[1] For example, on page 891, column 1, Schubert recites, "The activity even of well-designed siRNAs may be compromised severely when directed against a highly structured RNA."

expected to successfully use viral hairpins/miRNAs with secondary structure to target mRNAs based upon the teachings of Jacque in view of Hutvagner and Paillart.

In conclusion, the Applicant respectfully submits that (i) the cited references of Jacque in view of Hutvagner and Paillart do not teach or suggest the claimed invention, (ii) there is a lack of suggestion or motivation to combine the cited references; and (iii) the cited references do not provide a reasonable expectation of success. Accordingly, in view of the foregoing amendments and remarks the Examiner would be unable to establish a *prima facie* case of obviousness for the claimed subject matter under 35 U.S.C. § 103(a).

e. Double Patenting

On pages 12-14 of the Office Action, the Examiner provisionally rejects claims 1, 3, 6, 8, and 12 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 25-38 of copending Application No. 10/709,572 and claims 23-34 of copending Application No. 10/709,739. The Examiner also provisionally rejects claims 1, 3, 6, 8, 9, 12, 13, and 18 as allegedly being unpatentable over claims 1-4 and 12-16 of copending Application No. 11/511,035.

In view of the amendments and remarks made herein, Applicant respectfully submits that the only outstanding rejections are obviousness-type double patenting rejections, which will allow the Examiner to withdraw the provisional rejections and convert each to a double patenting rejection in the copending cases. In view of the instant application being filed earlier than the cited applications, Applicant respectfully requests that the obviousness-type double patenting rejection be withdrawn pursuant to MPEP 804.I.B.1.

4. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: June 18, 2007

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